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(54) **Covalently linked dimers of glycopeptide antibiotics**

(57) The present invention is directed to certain glycopeptide dimers in which two glycopeptide units are covalently linked to one another through a modifiable amine on a saccharide. These dimers are useful as an-

tibacterials, especially for the control of gram positive bacteria; the compounds are particularly useful for the control of resistant bacterial strains, such as vancomycin-resistant-enterococci ("VRE").

**EP 0 801 075 A1**

## Description

The present invention is directed to glycopeptide dimers covalently linked to one another through an amine function of an amino sugar. The invention is further directed to antibacterial methods employing, and pharmaceutical formula-

tions comprising, such glycopeptide dimers.

Glycopeptides are a class of antibiotics; see, e.g., "Glycopeptide Antibiotics", edited by Nagarajan (Marcel Dekker, Inc., 1994). Two of them, vancomycin and teicoplanin, are sold as antibacterial products for the control of gram positive bacterial infections. Vancomycin, the earlier-discovered of the two, was used for several decades with no bacterial resistance emerging. However, in the late 1980s, resistance was detected (Lancet I, 1988, 57-88). Such resistance has increased in the years since then; see "Nosocomial Enterococci resistant to Vancomycin -- United States, 1989-1993", MMWR Morbid Mortal Wkly. Rep. (Centers for Disease Control and Prevention). Resistance can be to either or both of these antibiotics, and/or also to methicillin. Resistant organisms have become common in nosocomial settings, presenting special risks for immunocompromised persons. Resistant bacteria present a formidable challenge to society.

The present invention provides a new tool in the armamentarium for controlling resistant bacteria.

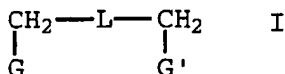
The present invention is directed to glycopeptide dimers which are covalently linked through an amine function of an amino sugar. The identity of the glycopeptide is not critical, except that it comprises a modifiable amine on a sugar. Preferred glycopeptides are those of the vancomycin type, also known as dalbaheptides (J. Antibiotics, Dec., 1989, page 1892).

Representative glycopeptides include:

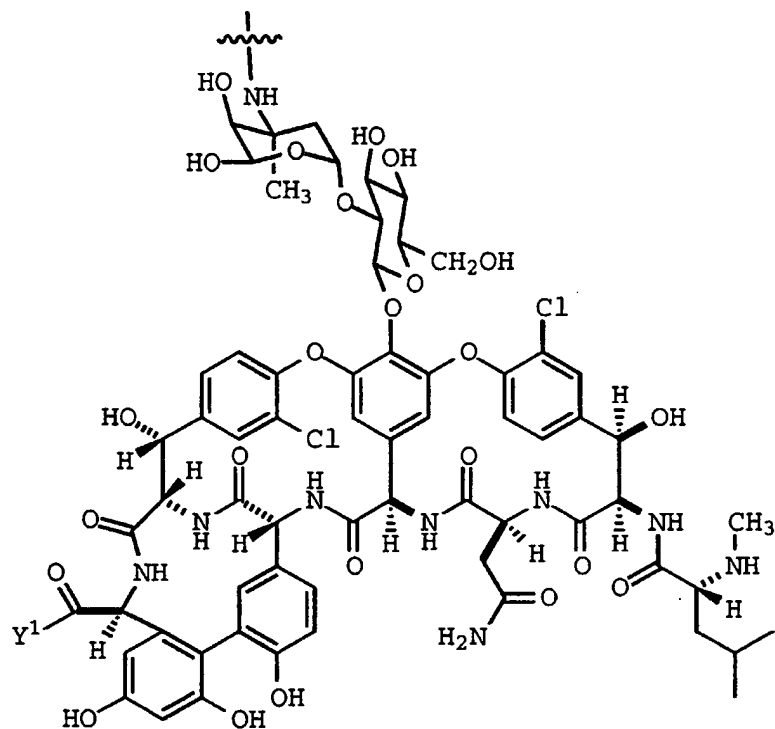
vancomycin,  
A82846A,  
A82846B,  
A82846C,  
PA-42867-A,  
PA-42867-C,  
PA-42867-D,  
A83850A,  
A83850B,  
actinoidin,  
avoparcin,  
galacardin,  
helevecardin, and  
M47767.

The linking group which functions to covalently link the two glycopeptide units is similarly not critical. The present dimers are most conveniently prepared by the reaction of the glycopeptide and a bisaldehyde, followed by reduction. Therefore, the linking group is the chemical unit internal to the aldehyde groups of any bisaldehyde.

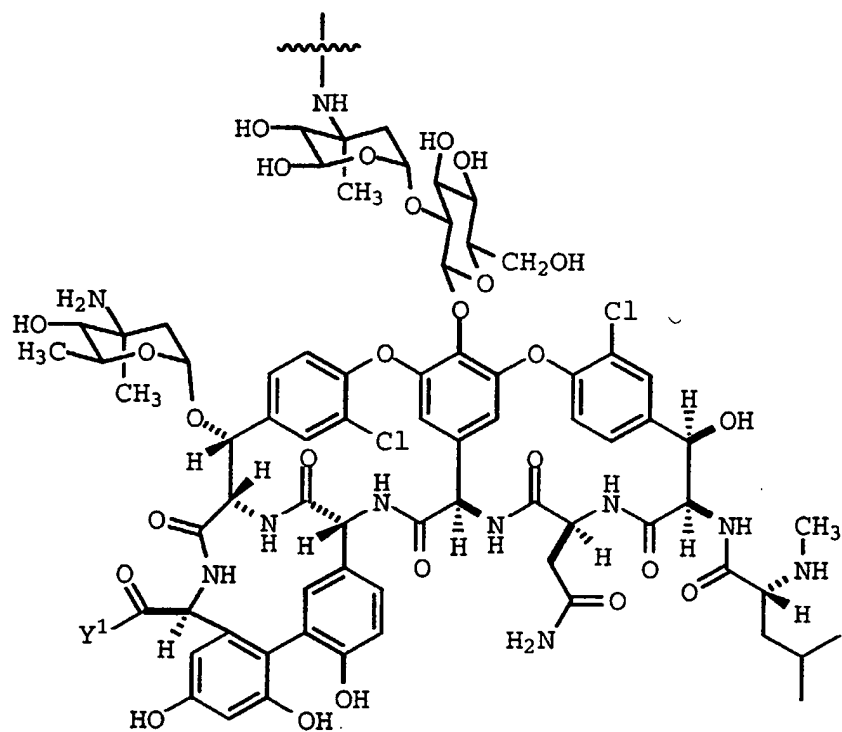
In one embodiment, the present invention is directed to specific dimer compounds defined by Formula I:



In the above formulae, each of G and G' is independently selected from the group consisting of deshydrovancomycin of the formula:



and deshydroA82846B of the formula:



wherein Y<sup>1</sup> is OH or



and Y<sup>2</sup> is defined as follows:

(1) each Y<sup>2</sup> independently represents

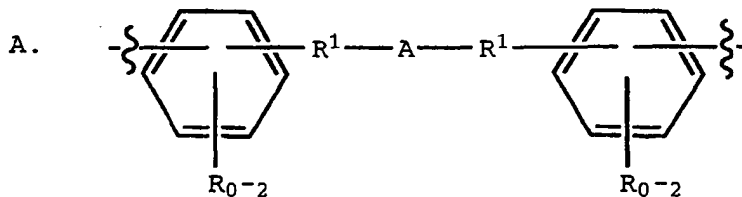
hydrogen,  
alkyl of C<sub>1</sub>-C<sub>10</sub>,  
cycloalkyl of C<sub>5</sub>-C<sub>6</sub>,  
cycloalkenyl of C<sub>5</sub>-C<sub>6</sub>,  
naphthyl,  
biphenyl,  
radical of the formula -Y<sup>3</sup>-(Y<sup>4</sup>)<sub>0, 1, or 2</sub>, wherein Y<sup>3</sup> is loweralkyl of C<sub>1</sub>-C<sub>6</sub> optionally substituted by from one to three substituents, each of which is independently selected from the group consisting of halo, nitro, cyano, alkoxy, haloalkyl, and haloalkoxy; and Y<sup>4</sup> is



wherein Y<sup>5</sup> is independently hydrogen or loweralkyl of C<sub>1</sub>-C<sub>4</sub>, or Y<sup>4</sup> is phenyl or phenyl substituted with from one to three substituents, each of which is independently halo, nitro, loweralkyl of C<sub>1</sub>-C<sub>4</sub>, cycloalkyl of C<sub>5</sub>-C<sub>6</sub>, loweralkoxy of C<sub>1</sub>-C<sub>4</sub>, haloloweralkyl of C<sub>1</sub>-C<sub>4</sub>, or haloloweralkoxy of C<sub>1</sub>-C<sub>4</sub> or

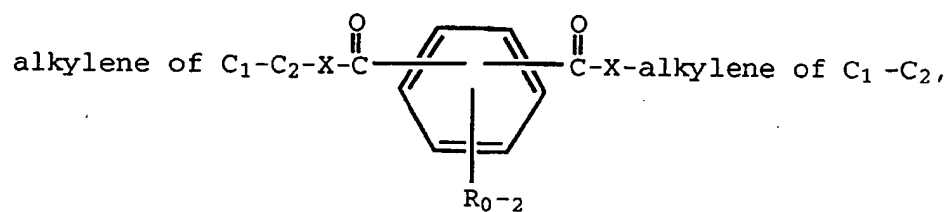
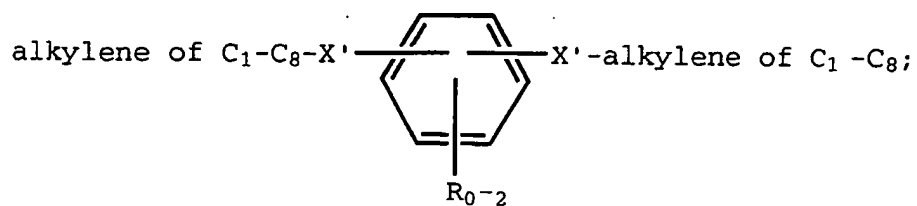
(2) one Y<sup>2</sup> is hydrogen and the other Y<sup>2</sup> is (2-furanon-3-yl); or

(3) both Y<sup>2</sup>s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C<sub>1</sub>-C<sub>2</sub>, loweralkoxy of C<sub>1</sub>-C<sub>2</sub>, phenyl, benzyl, or C<sub>1</sub>-C<sub>6</sub>-alkanoyl; and L is a divalent linking radical of the formula A:

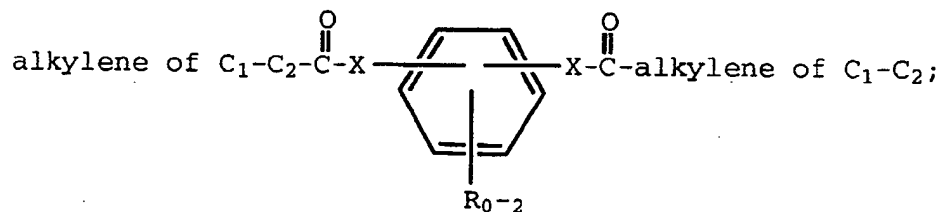


wherein A is: alkylene of C<sub>1</sub>-C<sub>16</sub>.

(alkylene of C<sub>1</sub>-C<sub>4</sub>-X')<sub>q</sub>-alkylene of C<sub>1</sub>-C<sub>4</sub>, wherein q is 1-3,



or

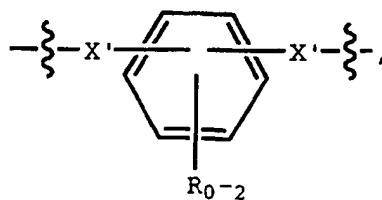


each R<sup>1</sup> is independently

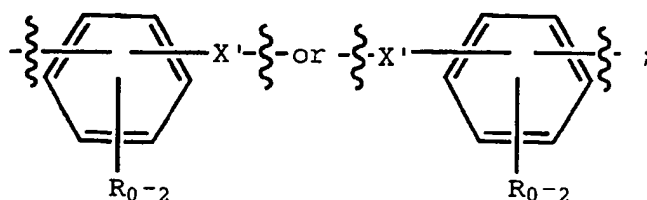
CH<sub>2</sub>,  
O,  
S,

-N-  
R<sup>2</sup>,

-X-C(=O)- or -C(=O)-X-,



or



wherein each R independently represents halo, loweralkyl of C<sub>1</sub>-C<sub>6</sub>, loweralkoxy of C<sub>1</sub>-C<sub>6</sub>, phenyl, or phenyl substituted by from 1 to 2 substituents, each of which is independently halo, loweralkyl of C<sub>1</sub>-C<sub>6</sub>, or loweralkoxy of C<sub>1</sub>-C<sub>6</sub>; each X is independently -O- or

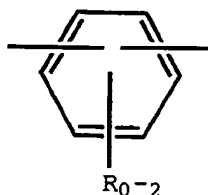


wherein R<sup>2</sup> is H or loweralkyl of C<sub>1</sub>-C<sub>4</sub>; and each X' is independently -O-, -S-, or



wherein R<sup>2</sup> is as defined above; or L is a divalent linking radical of the formula B:

30 B. -alkylene of C<sub>1</sub>-C<sub>8</sub>-R<sup>3</sup>-X\*-R<sup>3</sup>-alkylene of C<sub>1</sub>-C<sub>8</sub>-wherein X\* represents alkylene of C<sub>1</sub>-C<sub>4</sub> or a phenylene of the formula



wherein R is as defined above; and each R<sup>3</sup> is independently CH<sub>2</sub> or O. Salts of the foregoing dimers can be used.

In compounds of Formula I, the glycopeptide units, G and G', may be identical or different. Any "alkylene" of C<sub>2</sub> or higher can be straight chain or branched.

Certain compounds are preferred. Symmetrical compounds (G=G' and/or both R<sup>1</sup> are identical), are preferred for their more efficient synthesis.

Antibacterial activity is enhanced by employing preferred "L" groups. Preferences include the following, individually and in any combination:

50 L = a linking radical of formula A

L = a linking radical of formula B wherein the carbon attached to -CH<sub>2</sub>-G or to -CH<sub>2</sub>-G' is branched

R<sup>1</sup> = O

A = alkylene of C<sub>1</sub>-C<sub>16</sub>, especially straight-chain and especially C<sub>6</sub>-C<sub>12</sub>;

55 A = (alkylene of C<sub>1</sub>-C<sub>4</sub>-X')<sub>q</sub>-alkylene of C<sub>1</sub>-C<sub>4</sub>, especially wherein X'=O; the alkylene is -(CH<sub>2</sub>)<sub>2</sub>;

and q=2;

R = phenyl and substituted phenyl, especially chlorophenyl; and especially when R has this value on a phenyl ring within "A".

Other preferences will be apparent from the further teachings herein.

Representative dimers of Formula I are set forth in following TABLE 1.

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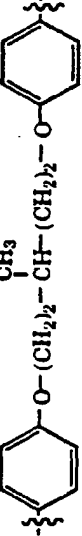


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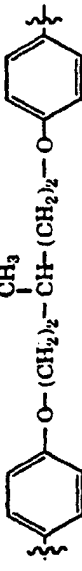
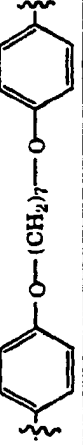




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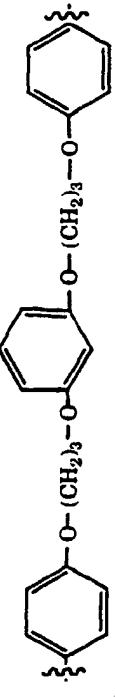
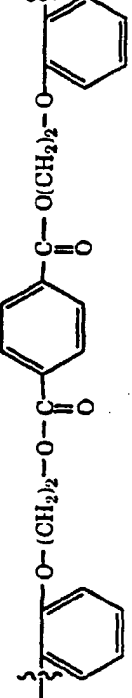
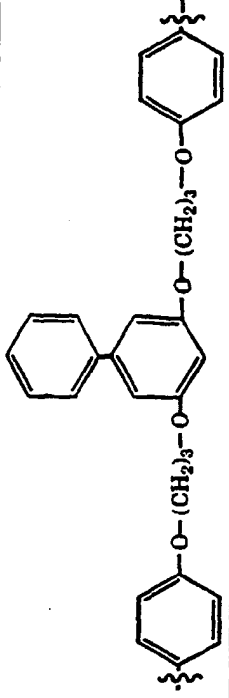
TABLE 1

Ex. #	G	G'	L	Name
1	Vanco	Vanco		1,2-ethanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
2	Vanco	Vanco		1,4-butanediyl-bis-[(oxy-2,1-phenylene)methylene]-bis-[vancomycin]
3	Vanco	Vanco		1,5-pentanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
4	Vanco	Vanco		1,5-pentanediyl-bis-[(oxy-3,1-phenylene)methylene]-bis-[vancomycin]
5	Vanco	Vanco		1,6-hexanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
6	Vanco	Vanco		[3-methyl-1,5-pentanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
7	Vanco	Vanco		1,7-heptanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
8	Vanco	Vanco		1,8-octanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]

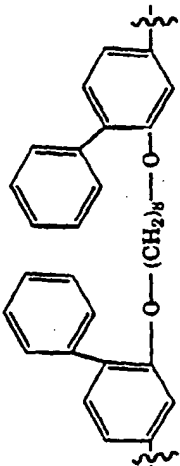
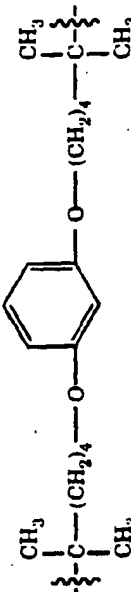
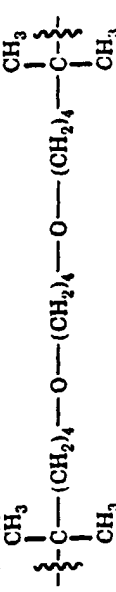

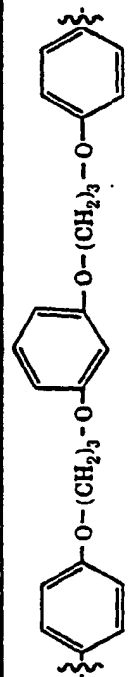
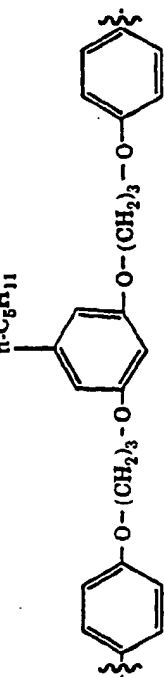


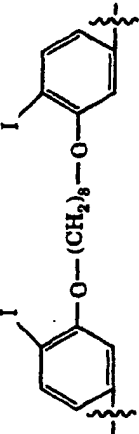
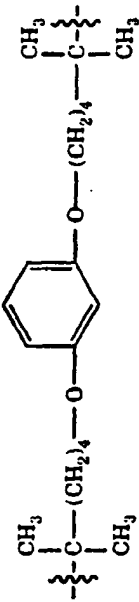
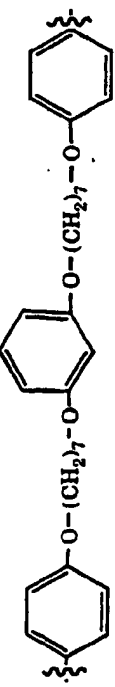
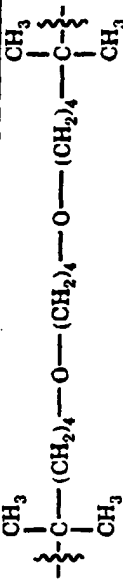
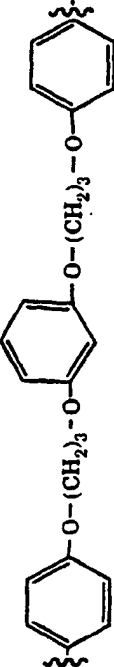
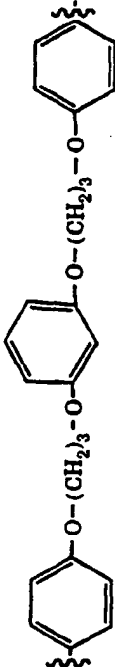
Ex. #	G	G'	L	Name
9	Vanco	Vanco		1,9-nonanediyl-bis-4,1-phenylene)-methylenel-bis-[vancomycin]
10	Vanco	Vanco		1,2-ethanediyl-bis-1,2-phenylene)-4,1-phenylene)-methylenel-bis-[vancomycin]
11	Vanco	Vanco		1,4-phenylene-bis-[(carbonyloxy-1,2-ethylenoxy-2,1-phenylene)-methylenel-bis-[vancomycin]
12	Vanco	Vanco		1,3-phenylene-bis-1,3-n-propyleneoxy-4,1-phenylene)-methylenel-bis-[vancomycin]
13	A82846B	Vanco		1,8-octanediyl-bis-4,1-phenylene-methylenel-bis-[vancomycin][A82846B]
14	A82846B	A82846B		1,3-propanediyl-bis-[(oxy-4,1-phenylene)-methylenel-bis-[A82846B]
15	A82846B	A82846B		1,4-butanediyl-bis-2,1-phenylene-methylenel-bis-[A82846B]
16	A82846B	A82846B		1,5-pentanediyl-bis-[(oxy-4,1-phenylene)-methylenel-bis-[A82846B]

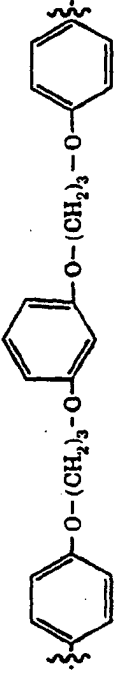
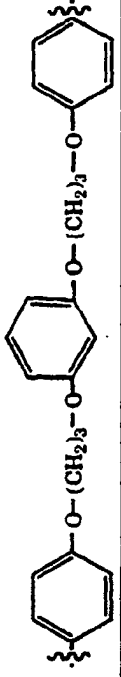
Ex. #	G	G'	L	Name
17	A82846B	A82846B		1,5-pentanediy1-bis-[(oxy-3,1-phenylene)-methylene]-bis-[A82846B]
18	A82846B	A82846B		1,6-hexanediy1-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
19	A82846B	A82846B		[3-methyl-1,5-pentanediy1]-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
20	A82846B	A82846B		1,7-heptanediy1-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
21	A82846B	A82846B		1,8-octanediy1-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
22	A82846B	A82846B		" · HCl salt
23	A82846B	A82846B		1,8-octanediy1-bis-[(oxy-3-n-pentyloxy-4,1-phenylene)methylene]-bis-[A82846B]
24	A82846B	A82846B		1,9-nonanediy1-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]

Ex. #	G	G'	L	Name
26	A82846B	A82846B		1,10-decanediyl-bis-[(oxy-4,1-phenylene)-bis-(A82846B)]
27	A82846B	A82846B		1,12-dodecanediyl-bis-[(oxy-4,1-phenylene)-bis-(A82846B)]
28	A82846B	A82846B		1,16-hexadecanediyl-bis-[(oxy-4,1-phenylene)-bis-(A82846B)]
29	A82846B	A82846B		1,2-ethanediyl-bis-[(oxy-1,2-ethylenedioxy-4,1-phenylene)methylene]-bis-[A82846B]
30	A82846B	A82846B		1,3-phenylene-bis-[(oxy-1,3-n-propylenedioxy-4,1-phenylene)methylene]-bis-[A82846B]
31	A82846B	A82846B		1,4-phenylene-bis-[(carbonyloxy-1,2-ethylenedioxy-2,1-phenylene)methylene]-bis-[A82846B]
32	A82846B	A82846B		1,3-[5-biphenyl]-bis-[(oxy-1,3-n-propylenedioxy-4,1-phenylene)methylene]-bis-[A82846B]

Ex. #	G	G'	L	Name
33	A82846B	A82846B		1,6-hexanediylbis[oxy- [4,4'-biphenylene]- methylene]bis (A82846B)
34	A82846B	A82846B		1,3-phenylenebis[oxy-1,5- n-pentyleneoxy [4,1- phenylene]methylene]bis (A82846B)
35	A82846B	A82846B		1,8-octanediylbis[oxy-4- phenyl-1,3,1-biphenylene]- methylene]bis (A82846B)
36	Vanco	Vanco		1,8-octanediylbis-[ (oxy- [3,1-phenylene] - methylene) - bis[vancomycin]
37	Vanco	Vanco		1,6-hexanediylbis[oxy- [4,4'-biphenylene]- methylene]bis- [vancomycin]
38	Vanco	Vanco		1,8-octanediylbis-[ (oxy- 4-iodo-3,1- phenylene]methylene]bis- [vancomycin]

Ex. #	G	G'	L	Name
39	Vanco	Vanco		1,8-octanediylbis-{[oxy-4-phenyl-1-{3,1-phenylene}methylene]bis-[vancomycin]}
40	Vanco	Vanco		1,3-phenylene-bis-[oxy-5-methyl-5,1-hexylene]bis-[vancomycin]
41	Vanco	Vanco		1,4-butanediylbis-[oxy-5-methyl-5,1-hexylene]bis-[vancomycin]
42	Vanco	Vanco		1,12-dodecanediylbis-[oxy-4,1-phenylene]bis-[vancomycin]
43	Vanco	Vanco		1,3-phenylene-bis-[oxy-1,3-n-propyleneoxy-4,1-phenylene]methylene]bis-[vancomycin] .3HCl salt
44	Vanco	Vanco		5-n-pentyl-1,3-phenylene-bis-[oxy-1,3-n-propyleneoxy-4,1-phenylene]methylene]bis-[vancomycin]

Ex. #	G	G'	L	Name
45	A82846B	A82846B		1,8-octanediylbis-[(oxy-4-iodo-3,1-phenylene)methylene]-bis-phenylene [A82846B]
46	A82846B	A82846B		1,3-phenylene-bis-[(oxy-5-methyl-5,1-hexylene)-bis-phenylene] [A82846B]
47	A82846B	A82846B		1,3-phenylene-bis-[(oxy-1,7-n-heptyleneoxy-4,1-phenylene)methylene]-bis-phenylene [A82846B]
48	A82846B	A82846B		1,4-butanediylbis-[(oxy-5-methyl-5,1-hexylene)-bis-phenylene] [A82846B]
49	A82846B	A82846B		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis-phenylene [A82846B]
50	A82846B, (3-dimethylamino propyl)-amide	A82846B		1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene]methylene-bis-phenylene [A82846B/A82846B, (3-dimethylaminopropyl) amide]

Ex. #	G	G'	L	Name
51	A82846B, (3- dimethyla mino propyl)- amide	A82846B, (3- dimethyl amino propyl)- amide		1,3-phenylenebis[oxy-1,3- n-propylene-oxy-4,1- phenylene)methylene]bis- [A82846B, (3- dimethylaminopropyl)- amide]
52	A82846B, desleucyl	A82846B, desleucyl		1,3-phenylene-bis-[(oxy- 1,3-n-propyleneoxy-4,1- phenylene)methylene]-- bis[desleucylA82846B]

The dimers of the present invention are prepared by reacting a glycopeptide with a bisaldehyde to form an intermediate Schiff base, which is subsequently reduced to obtain the dimers.

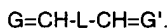
Many bisaldehydes are known compounds. They can be prepared by techniques known to those skilled in the art, per various references;

- 5  
J. Org. Chem., **26**, 474, (1961)  
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The reaction of bisaldehyde with glycopeptide is carried out in accordance with prior art condensations of amine and aldehyde to form Schiff bases, and their subsequent reduction.

25 Thus, the present condensation is typically conducted in a polar solvent, such as dimethylformamide or methanol, or a mixture of polar solvents. The reaction goes forward over a range of temperatures, such as from 25°C to 100°C, but is preferably conducted at temperatures of about 60°C to 70°C. The reaction is preferably conducted under an inert atmosphere, such as nitrogen or argon. The reaction requires two molecular proportions of glycopeptide and one molecular proportion of bisaldehyde.

30 The reaction yields a Schiff base of the formula

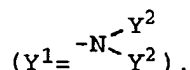


35 The Schiff base is subsequently reduced. Preferably, the reduction is conducted in the same reaction mixture in a polar solvent, and employing a chemical reducing agent. Metal borohydrides, such as sodium borohydride and sodium cyanoborohydride are preferred. The reaction goes forward over a range of temperatures, such as from about 25°C to about 100°C; preferably, the reaction is conducted at about 60°C to 70°C.

The product, or mixture of products, can be isolated and purified if desired in a conventional manner, such as by HPLC. Characterization of products is best accomplished by Fast Atom Bombardment Mass Spectroscopy (FAB-MS).

40 In addition to the foregoing synthetic route, compounds of the present invention can be prepared in an alternate route. In this alternate route, a dimer is prepared by the foregoing synthetic route, and further changes to the structure of the glycopeptide are made subsequently. This approach to synthesizing the present dimers is illustrated by Preparations 6-8 below. In Preparations 6-7, a dimer of the present invention is reacted with an amine to convert the acid of the glycopeptide to an amide

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In Preparation 8, a dimer of the present invention is subjected to Edman degradation to obtain the corresponding desleucyl dimer. Other modifications of the glycopeptide portion of a dimer can likewise be made. Techniques for such modifications are known to those skilled in the art; see Glycopeptide Antibiotics, supra, and references cited therein. This volume is incorporated herein by reference.

55 When it is desired to employ a salt, a compound of Formula I can be reacted with a mineral or organic acid or an inorganic base, in techniques well known to those skilled in the art. Pharmaceutically-acceptable salts are preferred.

The following examples report preparations of illustrative dimers.

The HPLC procedures reported in these examples were as follows:



Analytical ("Conditions A"): Reactions were monitored by analytical HPLC using a Waters  $\mu$ Bondapak C<sub>18</sub> column (3.9x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH<sub>3</sub>CN - 95% buffer to 80% CH<sub>3</sub>CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H<sub>3</sub>PO<sub>4</sub>.

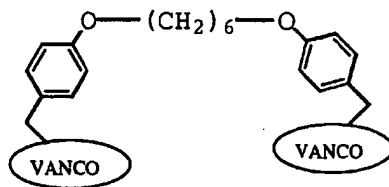
Preparative ("Conditions B"): Crude reaction mixtures were purified by preparative HPLC using a Waters C<sub>18</sub> Nova-Pak column (40x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH<sub>3</sub>CN - 95% buffer to 80% CH<sub>3</sub>CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H<sub>3</sub>PO<sub>4</sub>. The desired fractions were subsequently desalted with a Waters C<sub>18</sub> Sep-Pak (35 cc) followed by lyophilization. Alternatively, a buffer containing 0.1% TFA in H<sub>2</sub>O can be used, in which case the TFA salt is obtained directly after lyophilization.

Compounds were desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH<sub>3</sub>CN/H<sub>2</sub>O, CH<sub>3</sub>CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

#### Preparation 1:

#### Synthesis of Example 5, 1,6-hexanediylbis[(oxy-4,1-phenylene) methylene]bis[vancomycin]

(one-pot synthesis of vancomycin dimer)



A dry 100 mL round bottom flask was charged with vancomycin-HCl (250 mg, 0.168 mmol.), and 1,6-bis(4'-formylphenoxy)-n-hexane (101 mg, 0.310 mmol.). Anhydrous DMF (6 mL) was added to the flask and the resulting mixture was stirred under N<sub>2</sub> and heated to 70°C. After 3.5 hours, sodium cyanoborohydride (80 mg, 1.3 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction mixture was cooled, and stored at 0°C overnight.

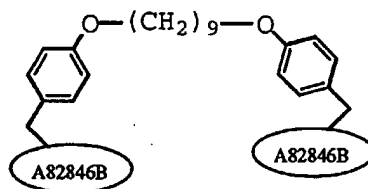
The reaction mixture was then concentrated *in vacuo* to give a residue which was re-dissolved in 1:1 H<sub>2</sub>O:CH<sub>3</sub>CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated *in vacuo* to ~ 1.5 mL, and desalted. After lyophilization, 1,6-hexanediylbis[(oxy-4,1-phenylene)methylene]bis[vancomycin] was obtained (24.3 mg, 0.008 mmol., 10.0 % yield) as a white powder.

HPLC (conditions A) retention time: 13.6 min.

FABMS shows peak of (M+6H) at 3195.

Preparation 2:Synthesis of Example 25, 1,9-nonanedylbis[(oxy-4,1-phenylene)methylene]bis[A82846B]

(one-pot synthesis of A82846 dimer)



A dry 100 mL round bottom flask was charged with A82846B-tri-acetate salt (278 mg, 0.157 mmol.), and 1,9-bis-(4'-formylphenoxy)-n-nonane (103.7 mg, 0.282 mmol.). Anhydrous DMF (15 mL) and anhydrous MeOH (15 mL) were added to the flask and the resulting mixture was stirred under  $N_2$  and heated to 70°C. After 3.5 hours, sodium cyanoborohydride (68 mg, 1.08 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour.

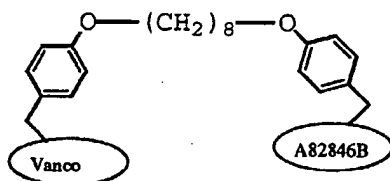
The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1  $H_2O:CH_3CN$  (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,9-nonanedylbis[(oxy-4,1-phenylene)methylene]bis[epivancomycin] was obtained (25.7 mg, 0.007 mmol., 9.3 % yield) as a white powder.

HPLC (conditions A) retention time: 14.9 min.

FABMS shows peak of (M+5H)<sup>+</sup> at 3522.

Preparation 3:Synthesis of Example 13, 1,8-octanedylbis[(oxy-4,1-phenylene)methylene][vancomycin] [A82846B]

(synthesis of hybrid dimer)



A dry round bottom flask was charged with vancomycin-HCl (75 mg, 0.052 mmol.), and  $N^4$ -(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B (50 mg, 0.026 mmol.) (see Preparation 4). Anhydrous DMF (6 mL) was added to the flask and the resulting mixture was stirred under  $N_2$  and heated to 70°C. After 5 hours, sodium cyanoborohydride (59 mg, 0.93 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction mixture was cooled, and stored at 0°C overnight.

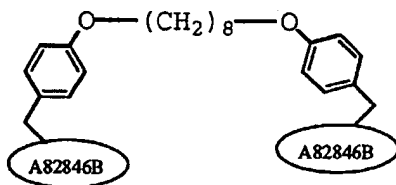
The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1  $H_2O:CH_3CN$  (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,8-octanedylbis[(oxy-4,1-phenylene)methylene][vancomycin][A82846B] was obtained (5.2 mg, 0.002 mmol., 7.6 % yield) as a white powder.

HPLC (conditions A) retention time: 14.5 min.

FABMS shows peak of (M+6H)<sup>+</sup> at 3364.

Preparations 4 & 5:Synthesis of Example 47, N<sup>4</sup>-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B, and Example 21, 1,8-octanediylbis[(oxy-4,1-phenylene)methylene]bis[A82846B]

(two-step synthesis of A82846 dimer)



A dry flask was charged with A82846B-tri-acetate salt (5.0 g, 0.003 mol.), and 1,8-bis(4'-formylphenoxy)-n-octane (1.93 g, 0.006 mol.). Anhydrous DMF (300 mL) and anhydrous MeOH (300 mL) were added to the flask and the resulting mixture was stirred under N<sub>2</sub> and heated to 70°C. After 3.75 hours, sodium cyanoborohydride (0.76 g, 0.012 mol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction was cooled and stored at 0°C overnight.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H<sub>2</sub>O:CH<sub>3</sub>CN (200 mL) and HOAc (5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, N<sup>4</sup>-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B was obtained (387.4 mg, 0.2 mmol., 6.6 % yield) as a white powder.

HPLC (conditions A) retention time: 19.9 min.

FABMS shows peak of (M+3H)<sup>+</sup> at 1932.

A dry flask was charged with N<sup>4</sup>-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B (20.0 mg, 0.01 mmol), and A82846B (32.9 mg, 0.021 mmol). Anhydrous DMF (3 mL) and anhydrous MeOH (3 mL) were added to the flask and the resulting mixture was stirred under N<sub>2</sub> and heated to 70°C. After 2 hours, sodium cyanoborohydride (5.0 mg, 0.079 mmol) was added in one portion, and the reaction mixture stirred an additional 0.25 hours.

The reaction mixture was then concentrated in vacuo to give a residue which was redissolved in 1:1 H<sub>2</sub>O:CH<sub>3</sub>CN (5 mL). The resulting solution was purified by preparatory HPLC (conditions D). The desired fraction, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,8-octanediylbis[(oxy-4,1-phenylene)methylene]bis[A82846B] was obtained (3.0 mg, 0.001 mmol, 8.6 % yield) as a white powder.

HPLC (conditions A) retention time: 13.6 min.

FABMS shows peak of (M+5H)<sup>+</sup> at 3508.

Preparations 6 & 7:Synthesis of Example 50, 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]A82846B/A82846B, (3-dimethylaminopropyl)amide, and Example 51, 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B, (3-dimethylaminopropyl)amide]

A dry round bottom flask was charged with 1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B] (50.0 mg, 0.014 mmol) and 1 mL DMSO. PyBOP (14.5 mg, 0.028 mmol) and 3-dimethylaminopropylamine (2.8 mg, 0.028 mmol) were added and the reaction was stirred at room temperature under nitrogen for one hour. The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H<sub>2</sub>O:CH<sub>3</sub>CN (5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A) were concentrated in vacuo to ~ 1.5 mL, and desalted as in previous examples. After lyophilization 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B, (3-dimethylaminopropyl)amide] (6.9 mg, 13.1% yield) and 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)-methylene]A82846B/A82846B, (3-dimethylaminopropyl)amide (6.6 mg, 12.8% yield) were obtained as white powders.

1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B, (3-dimethylaminopropyl)-amide]

HPLC (conditions A) retention time: 13.2 min.

FABMS shows peak of (M+9H) at 3761.

1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene]-methylene] A828468/A828468, (3-dimethylaminopropyl) amide HPLC (conditions A) retention time: 13.7 min.

5 FABMS shows peak of (M+6H) at 3674.

#### Preparation 8:

10 Synthesis of Example 52, 1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene] -bis [desleucylA82846B]

1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B] (165.8 mg, 0.0462 mmol) was dissolved in 15 mL H<sub>2</sub>O - pyridine (1:1 v/v) and treated with phenyl isothiocyanate (30 µl, 0.25 mmol). The resulting mixture was stirred at room temperature for 1.5 hours at which time HPLC analysis (conditions A) indicated complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* to give the crude bithiourea derivative as a white powder.

The crude thiourea intermediate was suspended in 15 mL CH<sub>2</sub>Cl<sub>2</sub>, cooled to 0°C, then treated with trifluoroacetic acid (0.20 mL). After 1 hour the reaction mixture was warmed to room temperature and stirred an additional 1 hour. An additional 0.20 mL trifluoroacetic acid was added and the mixture was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the crude product was purified by preparative HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A) were concentrated *in vacuo* to ~ 1.5 mL, and desalted as in previous examples to give 10.2 mg (7% yield) of 1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[desleucylA82846B] as a white powder.

FAB-MS: obtained 3333 (M+4)

25 HPLC retention time (conditions A): 15.1 min.

Details concerning the synthesis of all of the compounds of TABLE 1, as well as identifying characteristics, are presented in TABLE 2.

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TABLE 2

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB-MS M/Z	M+x H
1	1,2-bis(4-formylphenoxy)- n-ethane	11.5	1.86	3136	3
2	1,4-bis(2-formylphenoxy)- n-butane	11.8	0.79	3165	4
3	1,5-bis(4-formylphenoxy)- n-pentane	12.9	5.42	3178	4
4	1,5-bis(3-formylphenoxy)- n-pentane	13.0	4.08	3179	4
5	1,6-bis(4-formylphenoxy)- n-hexane	13.6	9.05	3195	6
6	3-methyl-1,5-bis(4-formylphenoxy)- n-pentane	13.5	4.54	3193	4
7	1,7-bis(4-formylphenoxy)- n-heptane	14.7	5.00	3207	5
8	1,8-bis(4-formylphenoxy)- n-octane	15.5	3.91	3219	2
9	1,9-bis(4-formylphenoxy)- n-nonane	16.4	4.41	3235	4
10	1,2-bis(2-(4-formylphenoxy)- ethoxy)ethane	12.3	1.89	3226	4
11	1,4-bis(2-(p-formylphenoxy)- ethoxy)carbonyl- benzene	13.0	10.50	3331	6
12	1,3-bis(3-(p-formylphenoxy)- n-propyloxy)- benzene	15.5	3.10	3300	4
13	1,8-bis(4-formylphenoxy)- n-octane	14.5	5.95	3364	4
14	1,3-bis(4-formylphenoxy)- propane	9.4	14.29	3436	4
15	1,4-bis(2-formylphenoxy)- n-butane	10.2	5.91	3452	5

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB-MS M/Z	M+x H
16	1,5-bis(4-formylphenoxy)- n-pentane	10.4	3.86	3466	5
17	1,5-bis(3-formylphenoxy)- n-pentane	11.3	22.41	3465	4
18	1,6-bis(4-formylphenoxy)- n-hexane	11.3	5.46	3478	4
19	3-methyl-1,5-bis(4-formylphenoxy)- n-pentane	11.3	8.14	3479	4
20	1,7-bis(4-formylphenoxy)- n-heptane	12.5	5.73	3494	5
21	1,8-bis(4-formylphenoxy)- n-octane	14.0	13.31	3508	5
23	1,8-bis(3-formylphenoxy)- n-octane	14.4	21.23	3508	5
24	1,8-bis(4-formyl-2-n-pentyloxy- phenoxy)-n-octane	20.8	16.91	3680	5
25	1,9-bis(4-formylphenoxy)- n-nonane	14.9	9.31	3522	5
26	1,10-bis(4-formylphenoxy)- n-decane	15.9	8.87	3535	5
27	1,12-bis(4-formylphenoxy)- n-dodecane	17.7	1.32	3565	6
28	1,16-bis(4-formylphenoxy)- n-hexadecane	20.4	4.05	3625	9
29	1,2-bis(2-(4-formylphenoxy)- ethoxy)ethane	10.2	6.28	3511	4
30	1,3-bis(3-(p-formylphenoxy)- n-propyloxy)- benzene	15.2	22.96	3589	5
31	1,4-bis(2-(p-formylphenoxy)- ethoxy)carbonyl- benzene	11.7	24.94	3615	5

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
32	5-phenyl-1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	16.8	12.88	3664	5
33	1,6-bis(4-(4-formylphenyl)-phenoxy)hexane	16.2	11.58	3633	5
34	1,3-bis(5-(4-formylphenoxy)-n-pentyloxy)-benzene	17.04	9.31	3645	6
35	1,8-bis(2-phenyl-5-formylphenoxy)-octane	18.3	10.83	3662	6
36	1,8-bis(3-formylphenoxy)-n-hexane	15.3	2.1	3221	4
37	1,6-bis(4-(4'-formylphenoxy)-phenoxy)-n-hexane	18.2	6.1	3347	6
38	1,8-bis(3-formyl-2-iodophenoxy)-n-hexane	22.9	2.2	3471	3
39	1,8-bis(2-phenyl-5-formylphenoxy)-n-octane	19.3	2.8	3374	4
40	1,3-bis(6-(2-dimethyl)-1-hexanaloxo)-benzene	15.5	8.2	3229	4
41	1,4-bis(6-(2-dimethyl)-1-hexanaloxo)-butane	13.5	6.1	3209	4
42	1,12-bis(4-formylphenoxy)-n-dodecane	21.6	6.8	3278	5
43	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	HCL SALT			
44	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-5-n-pentylbenzene	36.6	12.7	3660	8
45	1,8-bis(3-formyl-2-iodophenoxy)-n-octane	17.1	5.4	3762	6

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB-MS M/Z	M+x H
46	1,3-bis(6-(2-dimethyl)-1-hexanaloxy)-benzene	13.3	15.5	3516	5
47	1,3-bis(3-(p-formylphenoxy)-n-heptyloxy)-benzene	19.3	1.4	3701	6
48	1,4-bis(6-(2-dimethyl)-1-hexanaloxy)-butane	13.5	24.8	3495	4
49	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	HCL SALT			
50	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	13.7	12.8	3674	6
51	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	13.2	13.1	3761	9
52	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	15.1	7.0	3333	4

## \* Conditions A

The present glycopeptide dimers are useful for the treatment of bacterial infections. Therefore, in another embodiment, the present invention is directed to a method for controlling a bacterial infection in a host animal, typically a warm-blooded animal, which comprises administering to the host animal an effective, antibacterial amount of a glycopeptide dimer in which two glycopeptide units are covalently linked to one another through an amine function of an amino sugar. In this embodiment, the dimers can be used to control and treat infections due to various bacteria, but especially gram-positive bacteria. In a preferred embodiment, the dimers are used to control and treat infections due to bacteria resistant to existing antibacterials. For example, certain bacteria are resistant to methicillin, and yet others are resistant to vancomycin and/or teicoplanin. The present dimers provide a technique for controlling and treating infections due to such resistant bacterial species.

In carrying out this embodiment of the invention, the dimers can be administered by any of the conventional techniques, including the oral route and parenteral routes such as intravenous and intramuscular. The amount of compound to be employed is not critical and will vary depending on the particular compound employed, the route of administration, the severity of the infection, the interval between dosings, and other factors known to those skilled in the art. In general, a dose of from about 0.5 to about 100 mg/kg will be effective; and in many situations, lesser doses of from about 0.5 to about 50 mg/kg will be effective. A compound of the present invention can be administered in a single dose, but in the known manner of antibacterial therapy, a compound of the present invention is typically administered repeatedly over a period of time, such as a matter of days or weeks, to ensure control of the bacterial infection.

Also in accordance with known antibacterial therapy, a dimer of the present invention is typically formulated for convenient delivery of the requisite dose. Therefore, in another embodiment, the present invention is directed to a pharmaceutical formulation comprising a dimer of Formula I, in combination with a pharmaceutically-acceptable carrier. Such carriers are well known for both oral and parenteral routes of delivery. In general, a formulation will comprise a dimer in a concentration of from about 0.1 to about 90% by weight, and often from about 1.0 to about 3%.

The antibacterial efficacy of the present dimers is illustrated by following TABLES 3 and 4. The minimal inhibitory



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concentrations (MICs) were determined using a standard broth micro-dilution assay. TABLE 4 presents a comparison of the activity of illustrative compounds against representative vancomycin-resistant and vancomycin-sensitive enterococci (Enterococcus faecium and Enterococcus faecalis, mean geometric MIC (mcg/mL), as determined by the standard broth micro-dilution assay.

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TABLE 3  
In Vitro Antimicrobial Activity  
MIC (mcg/ml)/Compound

Organism	Vancomycin	A82846B	1	2	3	4	5	6	7
Staphylococcus aureus 446	0.5	0.25	4	16	8	8	4	4	2
Staphylococcus aureus 489	0.125	≤0.06	0.5	0.5	0.5	2	0.5	0.25	0.5
Staphylococcus aureus 447	0.5	0.25	16	>64	32	32	16	8	8
Staphylococcus aureus X400	0.5	0.125	1	1	2	2	1	1	1
Staphylococcus aureus X778	0.5	0.125	1	4	2	4	1	1	1
Staphylococcus aureus 491	1	0.25	0.5	0.5	0.25	2	0.25	0.5	0.5
Staphylococcus aureus S13E	0.5	0.125	2	2	2	4	1	2	0.5
Staphylococcus aureus S1199	0.5	0.125	4	4	32	4	2	4	1
Staphylococcus aureus S1199A	0.125	≤0.06	0.5	0.125	0.5	1	0.25	0.5	0.25
Staphylococcus aureus S1199B	0.5	0.125	4	4	16	4	2	4	1
Staphylococcus haemolyticus 109	16	1	8	4	8	8	4	8	2
Staphylococcus haemolyticus 419	8	4	16	>64	16	16	8	8	8
Staphylococcus epidermidis 270	16	0.25	8	>64	16	16	4	4	4
Enterococcus faecium 180	>64	8	0.25	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecium 180-1	0.5	0.125	0.5	1	0.5	1	0.25	≤0.06	≤0.06
Enterococcus faecalis 2041	2	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5
Enterococcus faecalis 276	1	0.125	0.25	0.25	0.5	0.25	0.5	0.5	1
Enterococcus gallinarum 245	4	0.25	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Haemophilus influenzae RD	>64	>64		>64		>64			
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.5		0.06	0.06	0.06	0.06	0.06	0.06	0.06
Streptococcus pneumoniae P1	0.25		0.06	0.06	0.06	0.06	0.06	0.06	0.06

TABLE 3  
In Vitro Antimicrobial Activity  
MIC (mcg/ml)/Compound

Organism	8	9	10	11	12	13	14	15	16
Staphylococcus aureus 446	8	1	8	16	8	8	4	4	8
Staphylococcus aureus 489	4	1	4	4	2	2	1	0.25	2
Staphylococcus aureus 447	32	4	16	64	8	16	16	64	>64
Staphylococcus aureus X400	4	1	4	8	2	4	2	0.5	2
Staphylococcus aureus X778	4	1	4	16	2	2	1	0.5	2
Staphylococcus aureus 491	2	0.5	1	0.25	2	1	0.25	0.125	0.5
Staphylococcus aureus S13E	8	2	4	8	4	4	2	1	1
Staphylococcus aureus SAl199	16	1	4	16	4	4	4	1	4
Staphylococcus aureus SAl199A	2	0.25	1	1	1	0.5	0.125	≤0.06	0.5
Staphylococcus aureus SAl199B	8	0.5	4	32	4	4	2	4	2
Staphylococcus haemolyticus 108	8	0.5	4	64	4	1	4	8	1
Staphylococcus haemolyticus 418	8	4	16	64	4	8	16	>64	32
Staphylococcus epidermidis 270	8	2	16	32	4	8	8	64	32
Enterococcus faecium 180	0.125	≤0.06	4	2	≤0.06	0.125	0.25	0.25	0.125
Enterococcus faecium 180-1	0.5	0.25	1	0.25		0.5	≤0.06	0.25	0.5
Enterococcus faecalis 2041	0.25	0.5	0.25	≤0.06	0.25	0.25	0.25	0.125	0.25
Enterococcus faecalis 276	2	1	1	0.5	1	1	0.5	0.5	1
Enterococcus gallinarum 245	0.25	0.06	0.125	0.06	0.06	0.06	0.06	0.06	0.25
Haemophilus influenzae RD	>64	>64	64			>64	>64		>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	8	0.06	0.06	0.06	0.06	0.06	0.06	0.06	1
Streptococcus pneumoniae Pl	4	0.06	0.06	0.06	0.06	0.06	0.06	0.125	1

TABLE 3  
In Vitro Antimicrobial Activity  
MIC (mcg/ml) /Compound

Organism	17	18	19	20	21	22	23	24	25
<i>Staphylococcus aureus</i> 446	4	8	4	4	8	4	2	2	4
<i>Staphylococcus aureus</i> 489	1	4	0.25	2	2	4	1	2	4
<i>Staphylococcus aureus</i> 447	>64	64	32	64	64	32	8	16	64
<i>Staphylococcus aureus</i> X400	1	2	0.5	2	2	4	1	2	2
<i>Staphylococcus aureus</i> X778	2	2	0.5	1	1	1	0.25	2	2
<i>Staphylococcus aureus</i> 491	0.5	0.25	0.25	1	2	2	1	1	2
<i>Staphylococcus aureus</i> S13E	1	2	1	2	1	2	4	2	4
<i>Staphylococcus aureus</i> S1199	1	2	1	4	1	2	2	2	4
<i>Staphylococcus aureus</i> S1199A	0.125	0.25	0.125	0.25	0.25	0.5	0.5	1	0.5
<i>Staphylococcus aureus</i> S1199B	1	1	2	2	1	4	1	2	4
<i>Staphylococcus haemolyticus</i> 105	0.5	0.5	8	2	16	4	4	2	2
<i>Staphylococcus haemolyticus</i> 419	8	16	32	32	8	16	4	4	16
<i>Staphylococcus epidermidis</i> 270	64	16	16	16	8	8	4	4	16
<i>Enterococcus faecium</i> 180	0.125	≤0.06	0.125	≤0.06	0.125	0.25	0.125	1	0.25
<i>Enterococcus faecium</i> 180-1	0.125	0.25	1	1	0.5	0.5		0.5	1
<i>Enterococcus faecalis</i> 2041	0.125	0.25	0.25	≤0.06	0.5	0.5	0.5	1	1
<i>Enterococcus faecalis</i> 276	0.125	0.125	1	0.25	1	1	1	2	1
<i>Enterococcus gallinarum</i> 245	0.06	0.06	0.06	0.06	0.06	0.06	0.125	0.5	0.25
<i>Haemophilus influenzae</i> RD	>64	>64		>64	>64	>64		>64	>64
<i>Escherichia coli</i> EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
<i>Streptococcus pyogenes</i> C203	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.25	0.25
<i>Streptococcus pneumoniae</i> P1	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.125

TABLE 3  
In Vitro Antimicrobial Activity  
MIC (mcg/ml)/Compound

Organism	26	27	28	29	30	31	32	33	34
<i>Staphylococcus aureus</i> 446	4	16	>64	16	1	1	16	16	2
<i>Staphylococcus aureus</i> 489	2	8	64	1	1	1	4	4	2
<i>Staphylococcus aureus</i> 447	>64	>64	>64	64	4	8	>64	>64	2
<i>Staphylococcus aureus</i> X400	1	16	32	1	1	0.5	4	8	1
<i>Staphylococcus aureus</i> X778	2	8	32	2	0.5	0.25	2	4	1
<i>Staphylococcus aureus</i> 491	2	8	16	≤0.06	0.25	≤0.06	2	4	0.5
<i>Staphylococcus aureus</i> S13E	2	8	64	4	0.5	0.25	8	8	1
<i>Staphylococcus aureus</i> S1199	2	8	64	2	1	0.5	8	8	2
<i>Staphylococcus aureus</i> S1199A	1	4	16	0.5	≤0.06	≤0.06	2	4	0.5
<i>Staphylococcus aureus</i> S1199B	2	8	64	4	1	0.5	8	16	2
<i>Staphylococcus haemolyticus</i> 105	4	32	32	0.25	0.25	0.25	4	2	0.5
<i>Staphylococcus haemolyticus</i> 419	16	64	64	>64	4	16	8	8	2
<i>Staphylococcus epidermidis</i> 270	8	32	64	32	1	2	16	8	1
<i>Enterococcus faecium</i> 180	0.5	1	8	0.25	0.125	1	1	1	0.5
<i>Enterococcus faecium</i> 180-1	1	1	8	0.5	0.125	≤0.06	2	2	0.25
<i>Enterococcus faecalis</i> 2041	1	4	8	0.125	0.25	≤0.06	2	2	0.125
<i>Enterococcus faecalis</i> 276	2	4	8	0.25	0.5	0.125	2	2	0.5
<i>Enterococcus gallinarum</i> 245	1	2	4	0.06	0.125	0.06	1	0.5	0.25
<i>Haemophilus influenzae</i> RD	>64	>64	>64			>64	>64		>64
<i>Escherichia coli</i> EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
<i>Streptococcus pyogenes</i> C203	4	0.5	64	0.06	0.06	0.06	0.5	2	≤0.06
<i>Streptococcus pneumoniae</i> P1	2	1	64	0.06	0.06	0.06	0.125	2	0.125

TABLE 3  
In Vitro Antimicrobial Activity  
MIC (mcg/ml)/Compound

Organism	35	36	37	38	39	40
<i>Staphylococcus aureus</i> 446	16	8	8	8	>64	8
<i>Staphylococcus aureus</i> 489	8	2	2	2	>64	2
<i>Staphylococcus aureus</i> 447	>64	16	16	32	>64	32
<i>Staphylococcus aureus</i> X400	4	4	2	4	>64	4
<i>Staphylococcus aureus</i> X778	4	4	2	4	>64	4
<i>Staphylococcus aureus</i> 491	2	1	1	2	>64	1
<i>Staphylococcus aureus</i> S13E	8	4	4	4	>64	8
<i>Staphylococcus aureus</i> S1199	32	8	4	4	>64	4
<i>Staphylococcus aureus</i> S1199A	8	1	2	2	>64	1
<i>Staphylococcus aureus</i> S1199B	8	16	2	4	>64	4
<i>Staphylococcus haemolyticus</i> 109	2	2	8	2	>64	2
<i>Staphylococcus haemolyticus</i> 419	16	8	16	16	>64	32
<i>Staphylococcus epidermidis</i> 270	8	4	8	8	>64	8
<i>Enterococcus faecium</i> 180	2	<.06	1	2	8	0.25
<i>Enterococcus faecium</i> 180-1	1	0.25	1	1	8	0.5
<i>Enterococcus faecalis</i> 2041	2	0.5	2	2	16	<.06
<i>Enterococcus faecalis</i> 276	4	0.25	1	4	32	0.5
<i>Enterococcus gallinarum</i> 245	1	0.06	1	4	8	0.06
<i>Haemophilus influenzae</i> RD		>64	>64	4	>64	
<i>Escherichia coli</i> EC14	>64	>64	>64	>64	>64	>64
<i>Streptococcus pyogenes</i> C203	1	0.06	1	16	8	0.06
<i>Streptococcus pneumoniae</i> P1	1	0.06	1	8	16	0.06

TABLE 3  
In Vitro Antimicrobial Activity  
MIC (mcg/ml)/Compound

Organism	41	42	43	44	45	46
<i>Staphylococcus aureus</i> 446	32	64	8	8	8	4
<i>Staphylococcus aureus</i> 489	1	32	1	4	2	1
<i>Staphylococcus aureus</i> 447	>64	>64	8	16	32	64
<i>Staphylococcus aureus</i> X400	4	32	2	8	2	1
<i>Staphylococcus aureus</i> X778	8	16	2	4	2	1
<i>Staphylococcus aureus</i> 491	1	8	1	2	2	0.5
<i>Staphylococcus aureus</i> S13E	8	>64	2	16	4	1
<i>Staphylococcus aureus</i> S1199	16	32	2	8	2	1
<i>Staphylococcus aureus</i> S1199A	8	16	0.5	1	1	0.125
<i>Staphylococcus aureus</i> S1199B	8	32	2	16	2	1
<i>Staphylococcus haemolyticus</i> 109	2	16	8	1	4	1
<i>Staphylococcus haemolyticus</i> 419	>64	64	8	8	4	32
<i>Staphylococcus epidermidis</i> 270	32	32	4	4	2	1
<i>Enterococcus faecium</i> 180	2	2	0.125	1	1	0.5
<i>Enterococcus faecium</i> 180-1	1	4	1	0.5	1	<0.06
<i>Enterococcus faecalis</i> 2041	0.25	4	0.25	2	1	<0.06
<i>Enterococcus faecalis</i> 276	0.5	8	0.25	2	1	0.5
<i>Enterococcus gallinarum</i> 245	1	1	0.06	1	1	0.06
<i>Haemophilus influenzae</i> RD	>64		>64		2	>64
<i>Escherichia coli</i> EC14	>64	>64	>64	>64	>64	>64
<i>Streptococcus pyogenes</i> C203	0.06	1	0.06	1	8	0.06
<i>Streptococcus pneumoniae</i> P1	0.06	2	0.06	2	4	0.06

TABLE 3  
In Vitro Antimicrobial Activity  
MIC (mcg/ml)/Compound

Organism	47	48	49	50	51	52
<i>Staphylococcus aureus</i> 446	16	8	0.5	2	4	8
<i>Staphylococcus aureus</i> 489	8	0.5	0.25	0.5	2	4
<i>Staphylococcus aureus</i> 447	>64	32	1	2	4	16
<i>Staphylococcus aureus</i> X400	16	1	0.5	1	4	8
<i>Staphylococcus aureus</i> X778	8	1	0.5	1	2	4
<i>Staphylococcus aureus</i> 491	8	0.5	<.06	0.5	2	2
<i>Staphylococcus aureus</i> S13E	32	4	1	1	2	16
<i>Staphylococcus aureus</i> SAl199	16	4	1	1	4	8
<i>Staphylococcus aureus</i> SAl199A	4	0.5	0.5	0.25	2	1
<i>Staphylococcus aureus</i> SAl199B	16	2	1	1	2	16
<i>Staphylococcus haemolyticus</i> 105	8	4	1	0.5	2	1
<i>Staphylococcus haemolyticus</i> 415	8	32	2	1	2	8
<i>Staphylococcus epidermidis</i> 270	8	4	0.5	1	1	4
<i>Enterococcus faecium</i> 180	2	1	0.25	1	2	1
<i>Enterococcus faecium</i> 180-1	0.5	0.25	<.06	0.25	0.5	0.5
<i>Enterococcus faecalis</i> 2041	2	0.25	<.06	0.5	0.5	2
<i>Enterococcus faecalis</i> 276	2	0.125	0.25	0.5	1	2
<i>Enterococcus gallinarum</i> 245	2	0.06	0.06	0.5	0.5	1
<i>Haemophilus influenzae</i> RD	>64	>64				
<i>Escherichia coli</i> EC14	>64	>64	>64	>64	>64	>64
<i>Streptococcus pyogenes</i> C203	2	0.06	0.06	0.125	0.5	1
<i>Streptococcus pneumoniae</i> PI	1	0.06	0.06	0.06	0.5	2



TABLE 4

In Vitro Activity Against Enterococci		
Cpd. Number	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
Vancomycin	282	3.9
A82846B	29	0.22
1	42	1.3
2	27	1.0
3	27	1.5
4	19	2.0
5	11	0.87
6	32	1.3
7	8.0	1.3
8	9.5	0.87
9	9.5	1.2
10	>90	3.0
11	38	1.7
12	4.0	0.66
13	9.5	1.2
14	>64	1.0
15	23	0.87
16	38	1.5
17	4.8	0.57
18	19	1.0
19	19	0.76
20	13	1.0
21	2.8	0.87
22	6.7	0.76
23	1.7	0.5
24	4.8	1.2
25	6.7	1.2
26	4.0	1.5
27	3.4	1.7
28	9.5	6.1
29	38	1.3
30	1.7	0.38
31	27	0.66
32	2.8	1.5
33	2.0	1.5
34	1.7	0.44
35	3.4	2.3
36	5.7	0.66
37	4.8	2.3
38	4.8	2.3
39	8	5.3
40	11.3	0.76
41	64	1
42	2.4	1.2
43	2.4	1.3
44	2	1.2
45	3.4	1.5
46	4.8	0.57
47	6.7	4

TABLE 4

In Vitro Activity Against Enterococci		
Cpd. Number	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
48	22	0.57
49	2	0.38
50	3.4	0.38
51	2.4	0.38
52	128	4.6

**Claims**

1. A glycopeptide dimer in which two glycopeptide units are covalently linked to one another through an amine function of an amino sugar, for use in antibacterial therapy.
2. A glycopeptide dimer in which two glycopeptide units are covalently linked to one another through an amine function of an amino sugar, for use in antibacterial therapy against vancomycin-resistant-enterococcus.
3. Use of a glycopeptide dimer according to either of Claims 1 and 2 in the manufacture of a medicament for treating a bacterial infection in a host.
4. Use according to Claim 3 in which both glycopeptide units of the dimer are A82846B.
5. Use according to Claim 3 in which both glycopeptide units of the dimer are vancomycin.



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number  
EP 97 30 2416

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	JOURNAL OF ANTIBIOTICS, vol. 49, no. 2, February 1996, TOKYO JP, pages 181-193, XP002037248 H LINSDELL ET AL.: "Dimerization of A82846B, vancomycin and ristocetin; influence on antibiotic complexation with cell wall model peptides" * the whole document *	1-12	C07K9/00 A61K38/14
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 115, no. 1, 13 January 1993, DC US, pages 232-237, XP002037249 U GERHARD ET AL.: "The role of the sugar and chlorine substituents in the dimerization of vancomycin antibiotics" * the whole document *	1-5	
P,X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 118, no. 51, 25 December 1996, DC US, pages 13107-13108, XP002037250 U N SUNDAM ET AL.: "Novel vancomycin dimers with activity against vancomycin-resistant enterococci" * the whole document *	1-5	
			TECHNICAL FIELD'S SEARCHED (Int.Cl.6)
			C07K A61K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 8 August 1997	Examiner Masturzo, P
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			

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